REMARKS

1. Objection to the abstract of the disclosure under MPEP 608.01(b)

The Examiner objected to the abstract of the disclosure under MPEP 608.01(b) for the reasons of record. Specifically, the Examiner has requested correction of the first line of the abstract that reads, "Methods and composition are provided for the treatment or prevention of drug-induced nephrotoxicity and related conditions." As such, please amend and replace the first line of the abstract with the following sentence:

Methods and compositions are provided for the treatment or prevention of drug-induced nephrotoxicity and related conditions.

2. Rejection of Claims 1, 5, 9, 13, 17 and 21 under 35 U.S.C. 112, first paragraph.

Claims 1, 5, 9, 13, 17 and 21 were rejected under 35 U.S.C. 112, first paragraph because the specification allegedly fails to enable the prevention of kidney disease for the reasons of record. In particular, the Examiner argued that the specification fails to provide information that would allow one of skill in the art to practice the claimed invention without undue experimentation, citing the 8 factors set forth by *In re Wands*.

Applicant respectfully traverses the Examiner's rejection. At the outset, Applicant refers to paragraph [0049] which describes a procedure for treating rats with 2-hydroxyestradiol (2-OHE) and leaving some of the rats untreated. Further, paragraph [0055] of the specification discusses some results of rats that were treated with 2-OHE and rats that were not so treated. In particular, paragraph [0055] explains that 2-OHE reduced the PAN-induced mortality rate by 66%. Applicant submits that one of ordinary skill in the art would understand from this statistic that by treating the rats with 2-OHE, such treatment prevented kidney disease and subsequent death in many of the rats.

Further, Applicant submits that paragraph [0058] explains that PAN induces proliferation of glomerular mesangial cells and that this effect of PAN is inhibited by 2-OHE. Accordingly, one of ordinary skill in the art would understand from this disclosure

that administration of 2-OHE would prevent the aforementioned proliferation and thus prevent kidney disease.

Similarly, paragraphs [0059] and [0060] disclose that PAN induces glomerular and interstitial infiltration of inflammatory cells and this infiltration is attenuated by 2-OHE and PAN expands the extracellular matrix in the glomerular and that this adverse effect of PAN is attenuated by 2-OHE, respectively. Accordingly, Applicant submits that one of ordinary skill in the art would understand from this disclosure that administration of 2-OHE would prevent the aforementioned infiltration of inflammatory cells and the PAN induced expansion of the extracellular matrix in the glomerular, thus preventing kidney disease.

In referring to the 8 factors recited in *In re Wands,* the Examiner argued that the state of the prior art for prevention of nephropathy is underdeveloped. Regardless of the prior art, the Specification of the instant application sufficiently and clearly explains experiments and methods for the prevention of nephropathy as discussed in the foregoing paragraphs of this response.

The Examiner also argues that no working examples are presented in the specification showing how to prevent nephropathies. Applicant respectfully disagrees with the Examiner's argument and submits, as previously explained, that examples of prevention may be found in paragraphs [0058], [0059] and [0060], among others. Furthermore, Applicant directs Examiner's attention to *In re Robins,* 429 F.2d 452, 457 (C.C.P.A. 1970) stating that "representative [samples] are not required by the statute and are not an end in themselves," and to *In re Long,* 368 F.2d 892, 895 (C.C.P.A. 1966) holding that the absence of a working example does not in and of itself compel the conclusion that a specification does not satisfy the requirements of section 112. As such, Applicant submits that Examiner's reliance on the working example argument is misplaced.

Finally, Examiner argues under factor 8 of the test that Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Applicant directs the Examiner's attention to cases that established the groundwork for the

In re Wands test, such as *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). In that case the inventors appealed a board decision holding undue experimentation would be required to determine which of thousands of possible combinations would work to produce hydroperoxides in their claimed catalytic process. First, the court determined that the claimed process was an "unpredictable" art. The dissent argued that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction*, whether the claimed product will be obtained" (emphasis in original) *In re Angstadt*, 190 USPQ at 222. The majority rejected this approach, arguing that under the dissent's standard, "all 'experimentation' is 'undue' since the term 'experimentation' implies that the success of the particular activity is *uncertain*. Such a proposition is contrary to the basic policy of the Patent Act", *In re Angstadt*, 190 USPQ at 219. The majority continued, "What the dissent seems to be obsessed with is the thought of catalysts which *won't* work to produce the intended result. Without undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them." (emphasis in original), *In re Angstadt*, 190 USPQ at 219. In accordance with the aforementioned legal principles, Applicant submits that upon reading the specification of the instant application, one of ordinary skill in the art would not need to undertake undue experimentation when attempting to practice the instant invention.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1, 5, 9, 13, 17 and 21 under 35 U.S.C. 112, first paragraph.

3. Rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a)

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 were rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. "Renoprotective effects of 2-hydroxyestradiol," *J Am Soc Nephrol* 12: 86A, 2001, for the reasons of record.

Initially, Applicant would like to point out that in order for an Examiner to establish a prima facie case of obviousness, the Examiner must show that each and every

one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When an independent claim is deemed nonobvious under 35 U.S.C. 103, then all claims depending therefrom are nonobvious as well. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicant respectfully submits that the Examiner has not overcome this burden. Specifically, all of the claims that were rejected by the Examiner recite that the conditions being "prevented" or treated are "drug-induced." Tofovic et al does not teach that the conditions being treated are drug-induced nor does Tofovic et al teach the prevention of such drug-induced conditions. Accordingly, the Examiner has not overcome the aforementioned burden since each and every one of the claim limitations of the instant invention were not taught or suggested by Tofovic et al.

Furthermore, the Examiner has the burden to prove that the prior art relied upon contains some suggestion or incentive that would motivate the skilled artisan to modify a reference. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001). Applicant submits that the Examiner has not satisfied this burden. All of the claims rejected by the Examiner in this office action contemplate preventing various drug-induced conditions. Tofovic et al does not suggest modifying its teachings in order to prevent the conditions mentioned nor does Tofovic et al suggest that its teachings would also be effective in treating or preventing drug-induced conditions. Therefore, Applicant respectfully submits that the Examiner has failed to show that Tofovic et al contains some suggestion or incentive to modify its teachings in order to prevent the conditions or prevent or treat the drug-induced conditions of the instant application.

Also, the Examiner has the burden of proving that the proposed modification of the prior art has a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Applicant submits that the Examiner has not satisfied this burden. The Examiner stated in the 35 U.S.C. 112, first paragraph rejection beginning on page 2 of this Office Action that this case involves "an

unpredictable and undeveloped art." (See (5) on page 4 of the instant Office Action). Therefore, Applicant fails to see how a person of ordinary skill in the art would have a reasonable expectation of success in modifying Tofovic et al to prevent the conditions of the instant applicantion nor treat or prevent the drug-induced conditions of the instant application. If the field of the instant invention is unpredictable as the Examiner submitted, a skilled artisan would not have a reasonable expectation of success in modifying Tofovic et al to prevent the conditions of the instant application nor would the skilled artisan have a reasonable expectation of success in treating or preventing the drug-induced conditions of the instant application.

In regard to claims 1, 2, 9, 13, 17 and 21, the Examiner argued that it is obvious that the teachings of Tofovic et al would treat the conditions listed in the above claims. However, with the statement made by the Examiner that this case involves "an unpredictable and undeveloped art," absent some motivation or suggestion found in Tofovic et al to modify its teachings, Applicant submits that it would not be obvious that its teachings would treat the conditions listed in the aforementioned claims.

Moreover, the Examiner stated that it is obvious that the teachings of Tofovic et al would "treat" the conditions listed in claims 1, 2, 9, 13, 17 and 21 but the Examiner did not discuss how it is obvious that the teachings of Tofovic et al would prevent the conditions listed in the claims. Since the claims rejected by the Examiner contemplate treating or preventing, the Examiner has not established that each and every one of the claim limitations of the instant invention were taught or suggested by Tofovic et al.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a).

4. Rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a)

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 were rejected under 35 U.S.C. 103(a) as being unpatentable over Xiao, S. et al. "Effects of estradiol and its metabolites on

glomerular endothelial nitric oxide synthesis and mesangial cell growth," Hypertension, 2001; 37; 645-650, for the reasons of record.

Initially, Applicant respectfully submits that the Examiner mis-characterizes the teachings of Xiao et al. The Xiao et al reference teaches that "...estradiol stimulates endothelial cell-derived nitric oxide (NO) synthesis...," in paragraph 2 on page 645. Furthermore, that same paragraph goes on to explain that, "...decreased NO synthesis...is associated with the pathogenesis of renal diseases..." The end of that paragraph hypothesizes that, "...estradiol may...reduce the rate of progression of renal disease by stimulating NO synthesis..." The conclusion reached by Xiao et al., is stated in the final paragraph on page 649 as, "...estradiol may protect against the progression of renal disease by inducing NO synthesis in GECs and inhibiting GMC growth..." It should be noted that all of the aforementioned information relates to estradiol and not estradiol metabolites such as 2-OHE.

Very importantly, Xiao et al., teaches that "[t]reatment with estradiol, but not 2-hydroxyestradiol and 2-methoxyestradiol, induced nitric oxide synthesis. *See* Abstract. Since Xiao et al. concluded that, "...estradiol may protect against the progression of renal disease ***by inducing NO synthesis in GECs and*** inhibiting GMC growth..." it would logically follow that since Xiao et al. teaches that 2-hydroxyestradiol does not induce NO synthesis, it would not protect against the progression of renal disease. (Emphasis added) Accordingly, Applicant submits that Xiao et al. teaches away from the instant application and thus cannot properly be used by the Examiner as support for a 35 U.S.C. 103(a) rejection.

The Examiner has the burden to prove that, among other things, the prior art relied upon contains some suggestion or incentive that would motivate the skilled artisan to modify a reference. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001). Applicant submits that the Examiner has not satisfied this burden. The Examiner argues that one having ordinary skill in the art would have been motivated to extend the findings of Xiao et al. to *in vivo* models of nephropathies to evaluate the renoprotective effects of these compounds. Applicant respectfully disagrees with

Examiner's argument. Applicant submits that since Xiao et al. teaches that 2-OHE does not induce NO synthesis and thus will not protect against the progression of renal disease, one of ordinary skill in the art would have no motivation to extend those findings since they teach away from the disclosure of the instant invention.

Also, the Examiner has the burden of proving that the proposed modification of the prior art has a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Applicant submits that the Examiner has not satisfied this burden either. Since Xiao et al. teaches that 2-OHE does not induce NO synthesis and thus will not protect against the progression of renal disease, Applicant submits that one of ordinary skill in the art would have no expectation of success in protecting against the progression of renal disease *in vivo*, as suggested by the Examiner.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a).

5. Rejection of Claims 3, 7, 11, 15, 19 and 23 under 35 U.S.C. 103(a)

Claims 3, 7, 11, 15, 19 and 23 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. and Xiao et al. as applied in the above rejections and in view of Nabahi (U.S. Patent No. 6, 103, 256), for the reasons of record. Specifically, the Examiner argues that Tofovic et al. and Xiao et al. do not teach a controlled release formulation but that Nabahi teaches a device that is capable of releasing the active ingredient on a daily basis for several months. Accordingly, the Examiner argues, it would have been obvious to combine the teachings of Tofovic et al. and Xiao et al. with Nabahi.

The Examiner submitted that Tofovic et al and Xiao do not teach a controlled release formulation but as Applicant has pointed out in each of the previous 35 U.S.C. 103(a) rejection sections, there are many other things that those references do not teach. Illustratively, Tofovic et al does not teach preventing the conditions of the instant application nor does it teach treating or preventing the drug-induced conditions of the instant application. Further, Xiao actually teaches away from the instant invention because it teaches that 2-hydroxyestradiol does not induce NO synthesis thus it would not protect

against the progression of renal disease. Since Xiao teaches away from the instant invention, it cannot properly be used in a 35 U.S.C. 103(a) rejection.

Nabahi teaches a very narrowly disclosed drug delivery device. Specifically, Nabahi explains the disadvantages associated with oral administration methods and with transdermal administration. (Column 1 lines 54 and 61). Also, Nabahi teaches a device wherein the concentration of active agent at the outer surface of the device is not substantially higher than the concentration of the active agent in the remainder of the device. (Column 4 lines 20 – 23 and Claim 1). The reference also discloses that convenient amounts of active agent present in the device are from 1 to 50% by weight. (Column 6 lines 62 – 63). The instant invention does not contain any such limitations. As an example, see paragraph [0045] of the instant specification describing that particular methods of administration of the instant invention include oral administration and transdermal administration. Accordingly, even if Tofovic et al and Nabahi are combined, the resulting combination would fall short of yielding the instant invention.

Furthermore, the modification suggested by the Examiner would cause the prior art relied upon to become inoperable so the necessary motivation to combine is lacking. As previously stated, the teachings of Nabahi explain the disadvantages of oral administration and transdermal administration and limit the use of its invention to intravaginal. (Column 1 lines 54 and 61). Such a device, if combined with the teachings of Tofovic et al, would render Tofovic et al inoperable since its teachings do not limit the administration of 2-hydroxyestradiol to intravaginal.

As previously stated in this Response, the Examiner has the burden to show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Even after combining Tofovic et al with Nabahi, the Examiner has not satisfied the aforementioned burden since neither of those references suggest or teach preventing the conditions of the instant invention nor do they teach or suggest treating or preventing the drug-induced conditions of the instant invention.

Requested Materials

As requested by the Examiner, Applicant has provided the abstract from the American Society of Nephrology meeting (J Am Soc Nephrol 12:86A) and said abstract is attached.

In view of the foregoing, Applicant respectfully submits that all rejections under 35 U.S.C. 112 and 35 U.S.C. 103(a) have been overcome. Accordingly, Applicant believes that Claims 1-24 are in condition for allowance.

Respectfully Submitted,

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